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herapeutic Response of Human Tumor Xenografts in Athymic Mice to Doxorubicin[1]

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STRACT

n order to establish the usefulness of the human tumor-nude use system as a predictive screen for anticancer agents, 17 nors (3 breast, 3 colon, 3 lung, 3 melanoma, 2 ovary, 1 state, 1 sarcoma, and 1 larynx), serially transplantable in ymic mice, were used to study antitumor activity of doxo- icin (Adriamycin). BALB/c nude mice were treated i.v. on weekly basis for 3 to 4 weeks, starting when the tumor ume became relatively large (advanced stage of tumor treat- nt). All the tumors except lung tumor T 293 showed a 90 to 0% tak rate and stable growth.

Doxorubicin, at dose levels of 6 and 10 mg/kg/injection i.v. ery week for 3 weeks, showed significant activity against all the three breast tumors studied. As was expected on the sis of clinical data, doxorubicin showed no antitumor activity ainst the three different colon tumors. In the case of lung nors, statistically significant activities against oat cell carci- ma T 293 and epidermoid carcinoma T 222 were observed. contradiction to clinical data, doxorubicin was found to have nificant activity against various melanomas studied and ght but not statistically significant activity against ovarian nor T 17. Experimental results obtained using doxorubicin ainst prostate, sarcoma, and larynx tumors also parallel the ported clinical data.

TRODUCTION

Human tumors transplanted into athymic mice (nude) do not mpletely represent the real human situation but are more sely akin to the human situation than are the murine tumors ed in primary screening studies; thus, they provide a unique del system for screening anticancer agents. In order to ablish the usefulness of the nude mouse-human tumor xen- raft system as a predictive screen for anticancer agents, it necessary to demonstrate that clinically active (or inactive) ugs retain the same level of antineoplastic activity (or inactiv- against similar tumor types implanted as xenografts in ymic mice, as in the clinical patients.

The limited number of studies of antitumor drug activity on nan tumors xenografted into athymic mice suggest that the ponse of such tumors to antitumor drugs is identical to the ponse of the patients of origin (22-24, 29, 33). We plan to t various clinically active drugs (in single and in combination chemotherapy) against different types of human tumors which have been transplanted into athymic mice. To that end, we have studied the antitumor activity of DX[4] (Adriamycin), the most broad-spectrum single agent in cancer chemotherapy, against several human tumor xenografts, representative of some of the major classes of human cancer (breast, colon, lung, melanoma, ovary, prostate, sarcoma, and larynx).

The results of these studies indicate that the nude mouse-human tumor system offers a great potential for the identification of new anticancer agents of clinical interest.

MATERIALS AND METHODS

Athymic Mice. All the animals used in these studies were 8- to 12-week-old female congenitally athymic BALB/c nude mice, homozygous for the *nu/nu* allele, bred in our laboratory. The colony of the mice was developed from breeding stock obtained from Laboratory Animal Breeding and Research Center G1, Ry, Denmark. As previously described (34, 35), the mice were maintained in isolation in autoclaved cages with polyester fiber filter covers, but not under germ-free or specific-pathogen-free conditions; all food, water, and bedding were sterilized. Every 3 months, for 3 weeks, piperazine hexahydrate, (1.3 mg/liter) was added to the drinking water to eliminate the intestinal nematodes normally present in mice, which might increase the T-cell-like activity in nude mice (2). At the end of the treatment, the mice were checked for the presence of further parasites.

Tumors. Human tumors, representative of some of the major classes of human cancer, were established by inoculation of fresh tumor tissue from patients into nude mice in our laboratory, as previously described (34, 35). Tumor tissue specimens obtained from the surgeon were transplanted into BALB/c *nu/nu* mice within 2 to 3 hr of resection. These specimens were rinsed with sterile medium containing antibiotics and then cut in small pieces for s.c. implantation. For serial transplantation, the tumor mass was removed under sterile conditions, separated from the capsule, minced in sterile medium containing antibiotics, and then, through two 18-gauge needles, inoculated s.c. on the backs of nude mice (0.2 ml/mouse). The number of previous passages ranged from 3 to 25 at the time of the study. The tumor take rate for all the tumor lines approached 90 to 100%, except for the lung tumor T 293, in which the take rate was approximately 40%. The donor patients had not been treated with DX before the surgery. Histological appearance of the serially transplanted tumors was identical to that of the original tumors. The growth curves of the studied tumors are shown in Chart 1, and the main characteristics of

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[4] The abbreviations used are: DX, doxorubicin; LDH, lactic dehydrogenase; T/C%, mean of relative tumor volume in treated mice/mean of relative tumor volume in control mice × 100.

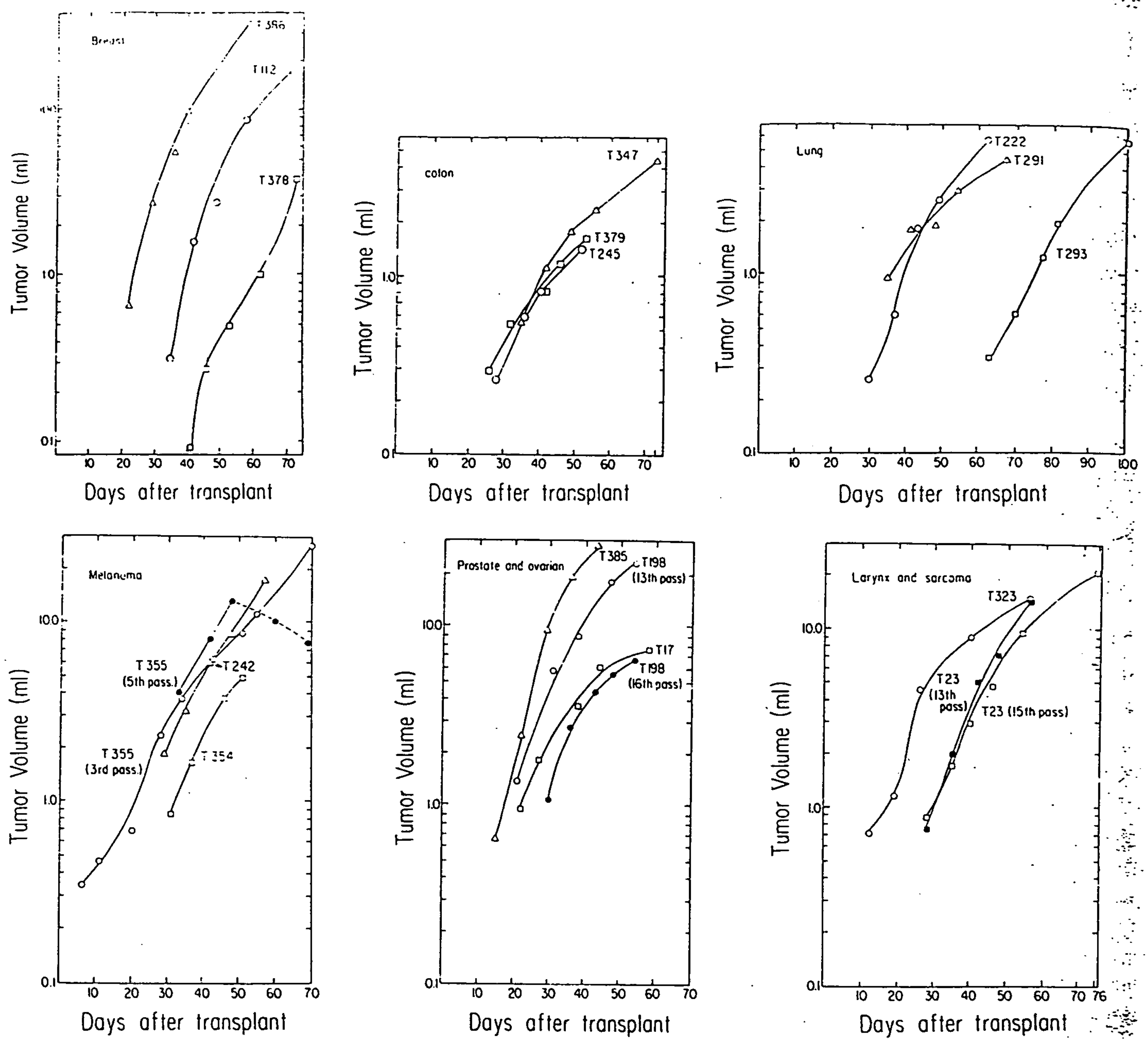

Chart 1. Growth of human tumors xenografted into nude mice. Each *point,* mean of 6 to 10 tumors.

these tumors are listed in Table 1. Individual growth of xenografts shows considerable variation (Chart 2); converting tumor volume measurements from absolute to relative values allows for easier visualization of antineoplastic activity of the drugs and standardized the tumor size at the start of the treatment.

Tumor Quantity of LDH Isoenzyme. The levels of mouse LDH and human LDH were quantitated in the tumor tissue transplanted into nude mice. Briefly, 4 tissue samples were taken, one from the tumor capsule, one from the portion immediately below the capsule, one from the core of the tumor, and one from the tissue between the capsule and the core. The tissue samples were homogenized separately and then centrifuged; the supernatants were collected and assayed for LDH activity using the pyruvate-to-lactate conversion procedure (NADH → NADT). Electrophoresis was carried out by determination of LDH isoenzymes in tumor supernatants using a Corning 72 fluorometer/densitometer. Human LDH standard was derived from human liver, and the mouse LDH standard was derived from corresponding BALB/c nude mouse liver. Twenty percent was arbitrarily fixed as the maximum allowable amount of mouse LDH in the tumor tissue sample that was taken from tumor core. The sample was not used if mouse LDH was more than 20%.

Treatment and Evaluation of Chemotherapeutic Effect. DX hydrochloride (supplied by Farmitalia Carlo Erba, Milano, Italy, and by Adria Laboratories, Columbus, Ohio) was dissolved in distilled wat r at a concentration such that the dose could be given in a volume of 0.1 ml/10 g body weight and was always administered i.v. weekly for 3 to 4 weeks. Because individual growth of implanted tumors shows great variability, we cannot

Table 1

Characteristics of human tumors grown in athymic mice

Tumor	Tissue of origin	Histopathological characteristics	No. of passages[a]	% of mouse LDH activity[b]
T 112	Breast	Infiltrating and intraductal breast carcinoma	16	20
T 386	Breast	Infiltrating ductal carcinoma (pseudomedullary type)	6	0
T 378	Breast	Carcinoma with chondroid change	3	0
T 245	Lymph node	Adenocarcinoma (metastatic from colon)	12	16.5
T 347	Colon	Adenocarcinoma	4	7.5
T 379	Colon	Adenocarcinoma	3	9.3
T 222	Lung	Epidermoid carcinoma	21	14
T 291	Lung	Adenocarcinoma	11	5
T 293	Sternum	Oat cell carcinoma	18	5
T 242	Lymph node	Malignant melanoma	25	9
T 354[c]	Melanoma	Amelanotic malignant melanoma	5	7
T 355[c]	Melanoma	Malignant melanoma	3	10
			4	6
T 17	Ovary	Cystoadenocarcinoma	13	10
T 385	Ovary	Adenocarcinoma	3	0
T 198	Prostate	Adenocarcinoma	13	13
			16	0
T 23	Shoulder	Undifferentiated sarcoma	13	14
			15	4
T 323	Larynx	Well-differentiated epidermoid carcinoma with parakeratosis	10	10

[a] At the time of the experiment.

[b] The percentage of mouse LDH detected in the tumors at the time of the experiment (see "Materials and Methods").

[c] Both specimens obtained from a large tumor of the same patient.

a homogeneous size of tumor in the large number of mice in our experiments. Therefore, the treatment was started ı transplant tumors became 0.5 to 1.5 cu cm. The DX s were selected on the basis of toxicity studies performed r laboratory on nontumorous BALB/c nude mice.

e mice were randomized in groups of 6 to 10 animals each ı the tumors reached palpable size. The tumors were sured weekly in 3 dimensions with a slide caliper. The r volume was calculated by the equation

$$\frac{1}{2} \pi d_1 \times d_2 \times d_3 = 1.57 \times d_1 \times d_2 \times d_3$$

d values are the experimental measurements (in mm) of umor length, width, and thickness. Each tumor volume then expressed in relative tumor volume (*RV*) by the ula

$$RV = Vx/Vi$$

e Vx is the volume at any given day and Vi is the tumor ıe at the start of treatment. The T/C% value was calcu- each time that the tumors were measured; the lowest was expressed as an optimal T/C% for each group. Each the tumors were measured, control relative tumor values compared with treated relative tumor volumes by Stu- s *t* test.

ILTS AND DISCUSSION

'enteen human tumors serially transplanted in athymic (3 breast tumors, T 112, T 378, and T 386; 3 colon 's, T 245, T 347, and T 379; 3 lung tumors, T 222, T 291, 293; 3 melanomas, T 242, T 354, and T 355; 2 ovary s, T 17 and T 385; one prostate tumor, T 198; one ma, T 23; and one larynx tumor, T 323) were tested for sensitivity to DX. The experimental results obtained were ared with clinical response of the above tumors to DX in .ts, as reported in the literature. As discussed below, the activity of DX against all the tumors studied, except the melanomas, is in good agreement with the clinical data. The results are briefly discussed here, divided according to the different classes of tumors studied, and are given in Tables 2, 3, and 4.

Breast Cancer. Clinically, breast cancer is responsive to a wide range of single agents, including DX (8). As a single agent, DX has a 40 to 50% response rate in metastatic breast cancer in patients previously untreated with chemotherapy (6, 9). In the nude mouse-human system, DX was tested on 3 breast tumors originating from 3 different patients and produced a delay in the tumor growth and a statistically significant decrease in the tumor volume in all 3 (Chart 3; Table 3). In case of breast tumor T 112, 2 dose schedules of DX were tested, 6 and 10 mg/kg/injection. Both the dose schedules produced statistically significant decreases in the tumor volume (T/C% = 6.9 and 11.8, respectively). The difference in activity of the low and high dose levels (6 and 10 mg/kg/injection) could be due to the fact that the 6-mg/kg group was inadvertently treated with 15 instead of 6 mg DX per kg per injection in the first treatment. This is probably the reason for the more effective inhibition of the tumor growth in the 6-mg DX per kg per injection dosage group. Sensitivity of breast tumors T 386 and T 378 to 10 mg DX per kg per injection every 7 days for 3 doses was also statistically significant (T/C% = 3.8 and 10.5, respectively). Chart 4 shows, in an illustrative experiment, the relative growth curves graphed for each individual mouse in the control groups and in the treated groups. The xenografts show considerable variations in both the controls and the treated groups. The individual curves show that the response of the tumors to DX treatment follows the same patterns in all the treated animals and the shape of the curves is parallel.

Colon Tumors. The majority of single agents are ineffective against colorectal tumors and those which are effective are only marginally so (5, 8). Among the useful drugs, DX is not included (5, 18). Three different human colon tumors transplanted into nude mice were used to test the DX activity. Chart

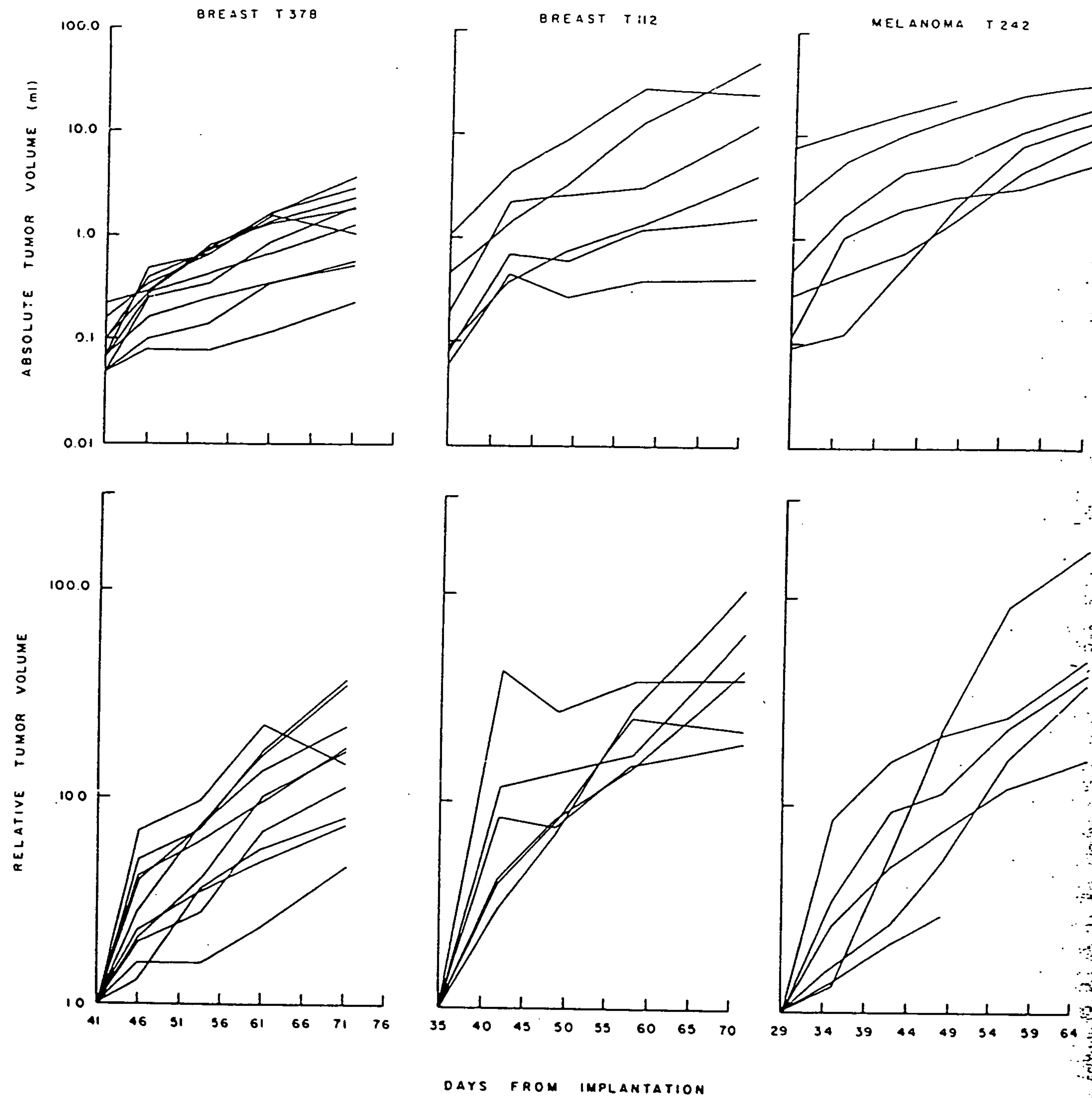

Chart 2. Absolute and relative tumor volume for human breast tumors T 112, T 378, and melanoma T 242. Each *curve* represents the growth of a tumor in an individual mouse.

5 and Table 3 show the results; DX administered i.v. at a dose of 10 mg/kg/injection every 7 days for 3 doses did not show any effect on the tumor growth. In other experiments involving screening of DX against 7 different colorectal tumors, we have observed similar results (26).

Lung Tumors. In a recent review of the literature on the use of DX as a single agent on lung cancer, Selawry (37) reported an overall response rate of 21% in 321 patients. The main histological types of bronchogenic carcinoma (epidermoid cardinoma, adenocarcinoma, and large- and small-cell carcinoma) respond differently to different antitumor drugs (12, 16, 37). Epidermoid carcinoma, the most common cell type (37), has an objective response to DX between 19% (37) and 35% (5); for small-cell carcinoma, the objective response is 25% (4, 16). The remaining cell types, adenocarcinoma and large-cell carcinoma, seem to be less responsive to DX (5). Chart 6 and Table 3 show the results of the chemotherapy performed with 3 different types (T 222 epidermoid carcinoma, T 291 adenocarcinoma, and T 293 oat cell carcinoma) of human lung tumors transplanted into nude mice. A statistically significant

Table 2
Experimental chemotherapy of human tumors heterotransplanted into nude mice

Tumor	T/C% after following doses of DX: 4.4 mg/kg/injection	6 mg/kg/injection	6.6 mg/kg/injection	10 mg/kg/injection
Breast				
T 112		+++[a,b]		+++[c]
T 378				+++[c]
T 386				+++[c]
Colon				
T 245				−
T 347				−
T 379				−
Lung				
T 222			++[a]	
T 291		−		−
T 293				++++[c]
Melanoma				
T 242		+		++[c]
T 354				+
T 355[d] (3rd passage)		++[c]		+++[c]
T 355 (4th passage)		±		+[c]
Ovary				
T 17		−		±
T 385				+
Prostate				
T 198 (13th passage)		−		+++[c]
T 198 (15th passage)				++[c]
Sarcoma				
T 23 (13th passage)	+		+++[c]	
T 23 (15th passage)				+++[c]
Larynx				
T 323		−		+

[a] Three i.v. treatments, one each week, starting when the tumor volume became relatively large.
[b] −, T/C% higher than 50%; ±, T/C% close to 50%; +, T/C% from 35 to 50%; ++, T/C% from 20 to 35%; +++, T/C% lower than 20%; ++++, regression of the tumor to a volume smaller than the volume at the start of treatment.
[c] Statistically significant as evaluated by Student's *t* test.
[d] Treatment started 6 days after tumor transplantation.

egression in the growth of the T 293 oat cell carcinoma (10 ng/kg/injection every 7 days for 3 doses; T/C% < 1, $p <$).01) and T 222 epidermoid carcinoma (6.6 mg/kg/injection :very 7 days for 3 doses; T/C% $= 20$, $p < 0.02$) was produced ›y DX injections. A slight and not statistically significant reponse was obtained on T 291 adenocarcinoma.

Malignant Melonoma. DX is inactive in the treatment of ıuman metastatic melanoma (4, 39). We tested the DX activity ·n 3 different human melanomas, derived from 2 different atients (Chart 7; Table 3). Treatment of T 242, a malignant ıelanoma that has metastasized to a lymph node, was started ·hen the tumors were in the advanced stage and produced a ose-dependent delay in tumor growth (T/C% $= 13$, $p < 0.05$). he chemotherapy of melanotic melanoma T 355 either was iven 6 days after the tumor implantation (early-stage tumor eatment), or was delayed until the tumor became relatively :rge (advanced stage of tumor treatment). The early-stage ımor was more sensitive than the advanced-stage tumor. Both ! the doses tested gave a dose-dependent statistically signif-:ant reduction in tumor growth, in early-stage tumors (6 mg/ g/injection: T/C% $= 32.7$, $p < 0.01$; 10 mg/kg/injection: /C% $= 7.8$, $p < 0.005$); whereas in the advanced stage of :mors, the DX activity was detected only at the higher dose vel (10 mg/kg/injection: T/C% $= 48.9$, $p < 0.02$). DX was ›t active against T 354 tumor.

The DX activity against the melanomas tested is quite surprising. The DX activity against the T 355 melanoma treated in the early stage could be explained on the basis that the growth fraction is larger, the vascular supply is better, and the response to the drug is better in small tumors (3, 20), but it is difficult to explain the experimental activity of DX on large tumors. Bellet *et al.* (3) have reported that 7 established human melanoma tissue-cultured cell lines heterotransplanted in nude mice and treated with DX were refractory to the treatment. However, Karakousis (30) has recently shown that high levels of DX produced by tourniquet infusion can cure human extremity melanomas. Two of the melanomas tested, T 354 and T 355, although obtained from a large tumor from the same patient, differ in their histological characteristics and also differ in their response to DX treatment. This suggests that heterogeneity of tumors could be a major cause of little sensitivity of some of the tumors to monochemotherapy and good response to combination chemotherapy.

Ovarian Tumors. A variety of drugs are active against ovarian cancer (15). DX as single agent is a useful drug in the treatment of ovarian carcinoma, in both previously untreated patients and in those who have failed to respond to alkylating agent therapy (5, 11, 15, 18). DX has a 33 to 38% overall response rate in ovarian cancer (1, 19). The experimental activity of DX tested against 2 different ovarian tumors (T 17

Table 3

Effect of DX on human breast, colon, lung, melanoma, and ovary tumors transplanted into nude mice[a]

Tumor	Dose (mg/kg/injection)	DTS[b]	Optimal T/C%	p[c]
Breast				
T 112[d]	6	34	6.9 (23)[e]	<0.01
	10		11.8 (23)	<0.01
T 386	10	21	3.8 (40)	<0.01
T 378	10	37	10.5 (20)	<0.01
Colon				
T 245	10	60	99 (8)	
T 347	10	34	90 (7)	
T 379	10	40	81 (15)	
Lung				
T 222	4.4	30	74.7 (19)	
	6.6		20 (19)	<0.02
T 291	6	35	70.4 (6)	
	10		77.9 (32)	
T 293	10	64	<1[f] (18)	<0.01
Melanoma				
T 242	6	29	49 (27)	
	10		13 (19)	<0.05
T 355[g]	6	6	32.7 (22)	<0.01
	10		7.8 (39)	<0.005
T 355	6	32	61 (9)	
	10		48.9 (15)	<0.02
T 354	10	29	44 (20)	
Ovary				
T 17	6	22	67.5 (36)	
	10		57.8 (36)	
T 385	10	16	47.6 (30)	

[a] Three i.v. treatments, one each week. Six to 10 mice were used in each experiment for both control and treated groups.
[b] DTS, days after tumor transplant that the treatment was started.
[c] Analysis performed between controls *versus* treated groups using Student's *t* test.
[d] The 6-mg/kg dosage group was inadvertently given an initial dose of 15 mg/kg/injection.
[e] Numbers in parentheses, day of evaluation after the start of treatment.
[f] Tumor volume became less than the initial tumor volume (regression).
[g] Treatment started 6 days after tumor transplantation. The dose schedule used was every 7 days for 4 doses.

Table 4

Effect of DX on human prostate, sarcoma, and larynx

Tumor	No. of transfers	Schedule of treatment[a]	Dose (mg/kg/injection)	DTS[b]	Optimal T/C%	p[c]
Prostate	13					
T 198		q7d × 4[d]	6	21	62.4	
			10		11.6	<0.01
	16					
		q7d × 3	10	30	31.7	<0.01
Sarcoma	13					
T 23		q7d × 4	4.4	28	38.9	
			6.6		19.8	<0.05
	15					
		q7d × 3	10	29	16.5	<0.01
Larynx	10					
T 323		q7d × 3	6	30	64.5	
			10		40.3	

[a] Three i.v. treatments, one each week. Six to 10 mice were used in each experiment for both control and treated groups.
[b] DTS, days after tumor transplant that the treatment was started.
[c] Analysis performed between controls *versus* treated groups using Student's *t* test.
[d] q7d × 3 or 4, every 7 days for 3 or 4 doses.

and T 385) transplanted into nude mice is shown in Chart 8 and in Table 3. The activity was slight and not statistically significant: T 17, T/C% = 57.8; and T 385, T/C% = 47.6.

Prostate, Sarcoma, and Larynx Tumors. Prostate cancer treatment is normally performed by surgery, radiation, and hormonal therapy in different sequences. The objective response rate to DX is 26 to 29% (21, 28, 31) in patients with prostate carcinoma who have failed treatment with hormones. DX was tested against prostate adenocarcinoma T 198 transplanted into nude mice in 2 different experiments (Chart 9; Table 4) involving tumors with different passage numbers, and it produced a delay in the tumor growth in both [T 198 (13th passage), 10 mg/kg/injection: T/C% = 11.6, $p < 0.01$; and 6 mg/kg/injection: T/C% = 62.4]. In another experiment performed with T 198 tumor, the response to DX treatment (10 mg/kg/injection) was slightly less than in the previous experiment (T/C% = 31.7, $p < 0.01$).

The first really useful drug found to be active against human adult soft tissue sarcomas was DX (7, 32); the response rate to DX of soft-tissue sarcoma is about 30% (7, 28, 32).

The DX treatment against T 23 human soft-tissue sarcoma transplanted into athymic mice was performed with 2 different schedules in 2 different experiments. DX administered at the dose of 6.6 mg/kg/injection twice a week for 2 weeks (Chart 10; Table 4) produced a dose-dependent statistically significant delay in the tumor growth: T/C% = 19.8, $p < 0.05$. In another experiment with T 23 sarcoma, administration of DX once a week for 3 weeks at the dose of 10 mg/kg/injection produced a statistically significant delay in the tumor growth: T/C% = 16.5, $p < 0.01$.

DX is active against head and neck carcinoma, but the literature data are generally expressed as an overall rate,

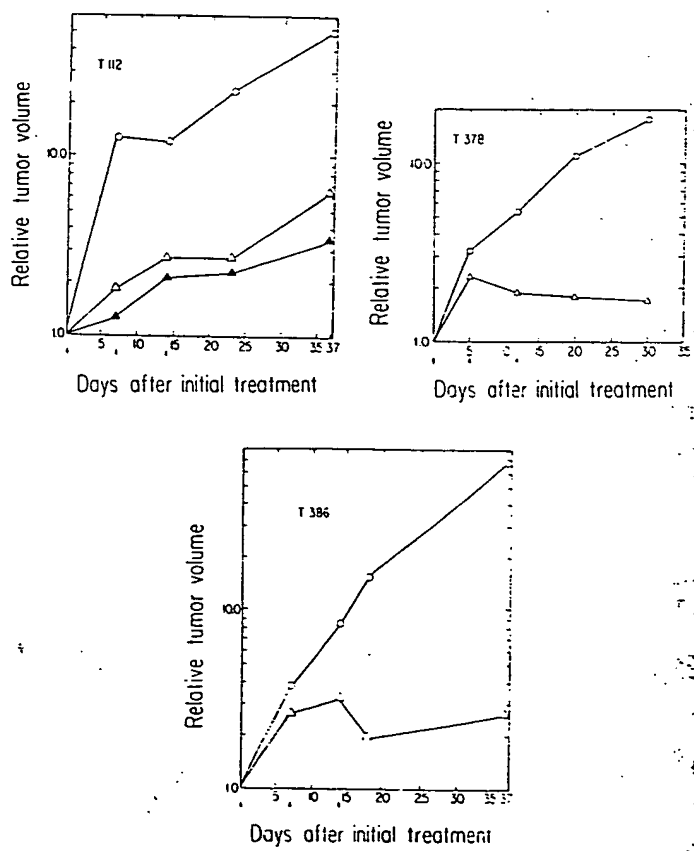

Chart 3. Response of T 112, T 386, and T 378 human breast tumors in nude mice to DX. O, controls; Δ, 10 mg/kg/injection; ▲, 6 mg/kg/injection. Relative tumor volume is the ratio of tumor volume at any given day to the tumor volume when the treatment was started. *Arrows*, treatment.

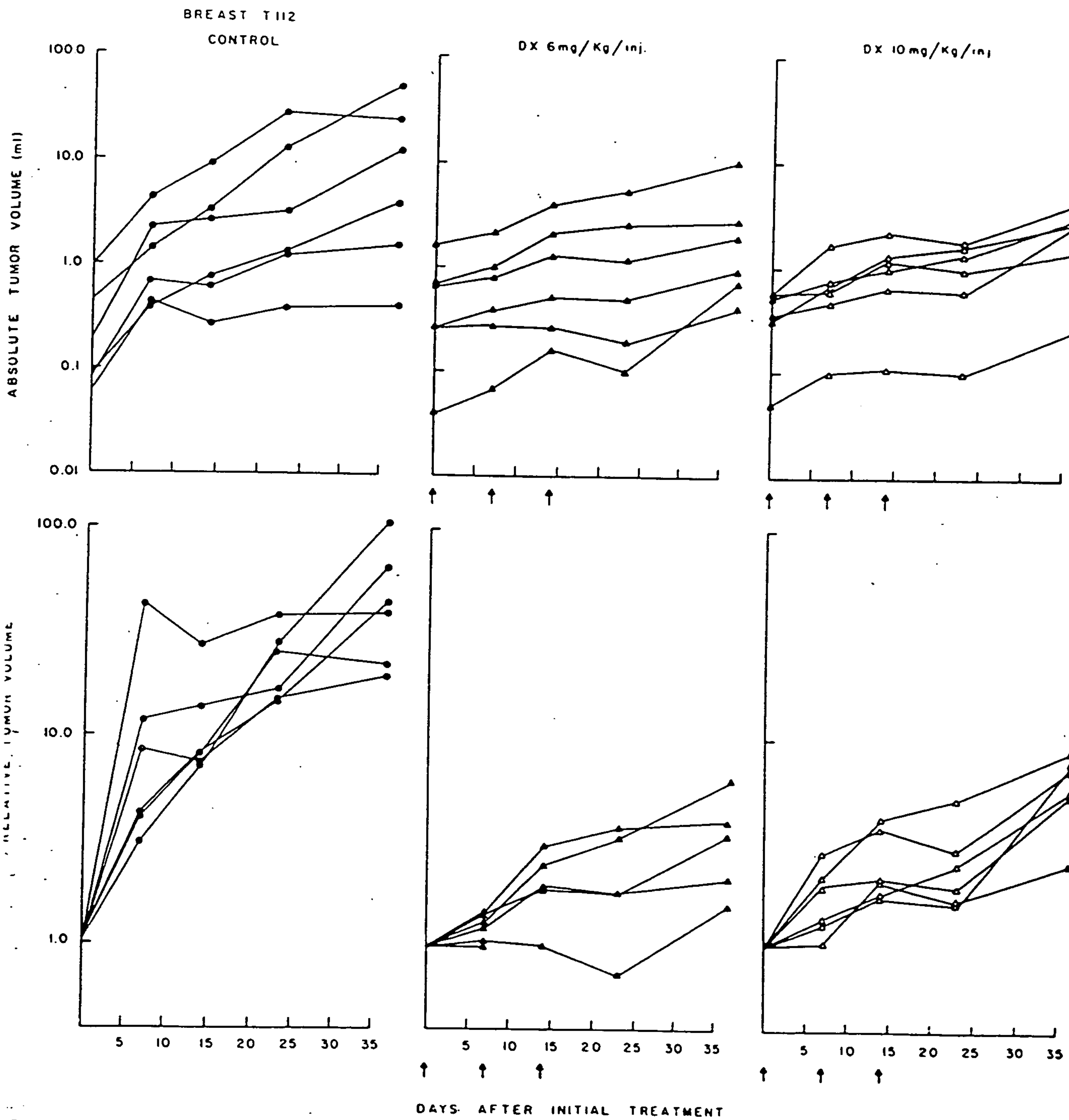

Chart 4. Response of T 112 human breast carcinoma in nude mice to DX reported as absolute and relative tumor volume. Each *curve* represents the growth of a mor after the i.v. treatment in an individual mouse. *Arrows*, treatment.

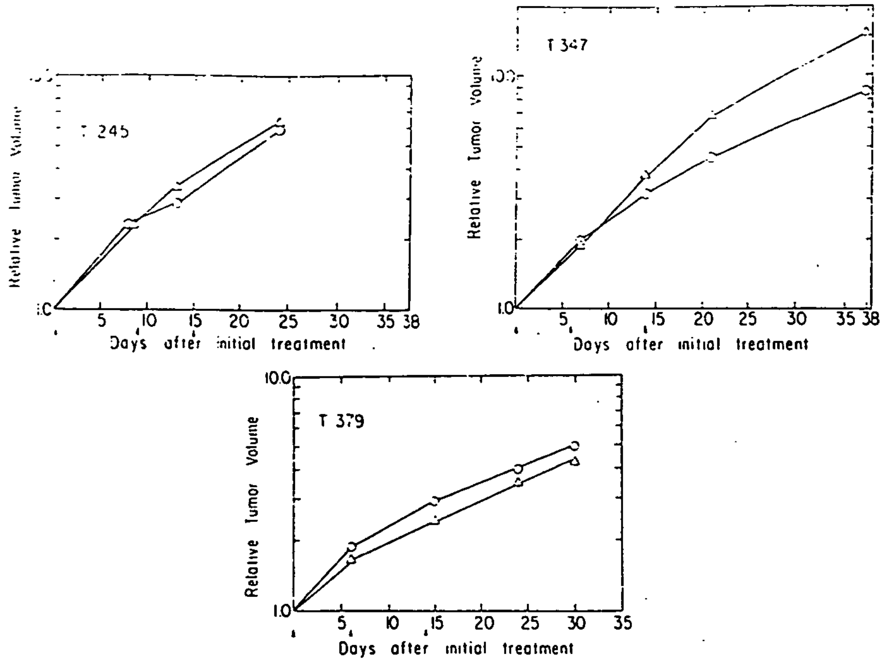

Chart 5. Response of T 245, T 379, and T 347 human colon tumors in nude mice to DX. O, controls; Δ, 10 mg/kg/injection. *Arrows*, treatment.

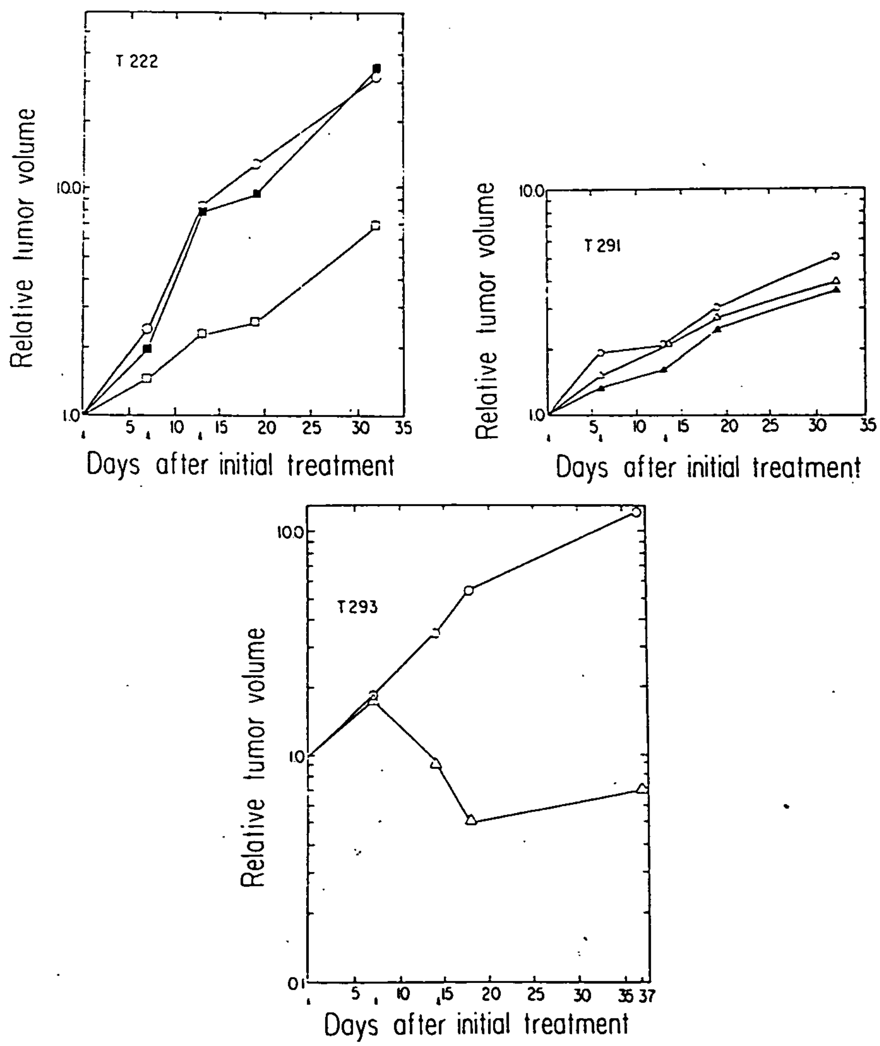

Chart 6. Response of T 222, T 291, and T 293 human lung tumors in nude mice to DX. O, controls; ■, 4.4 mg/kg/injection; ▲, 6 mg/kg/injection; □, 6.6 mg/kg/injection; Δ, 10 mg/kg/injection. *Arrows*, treatment.

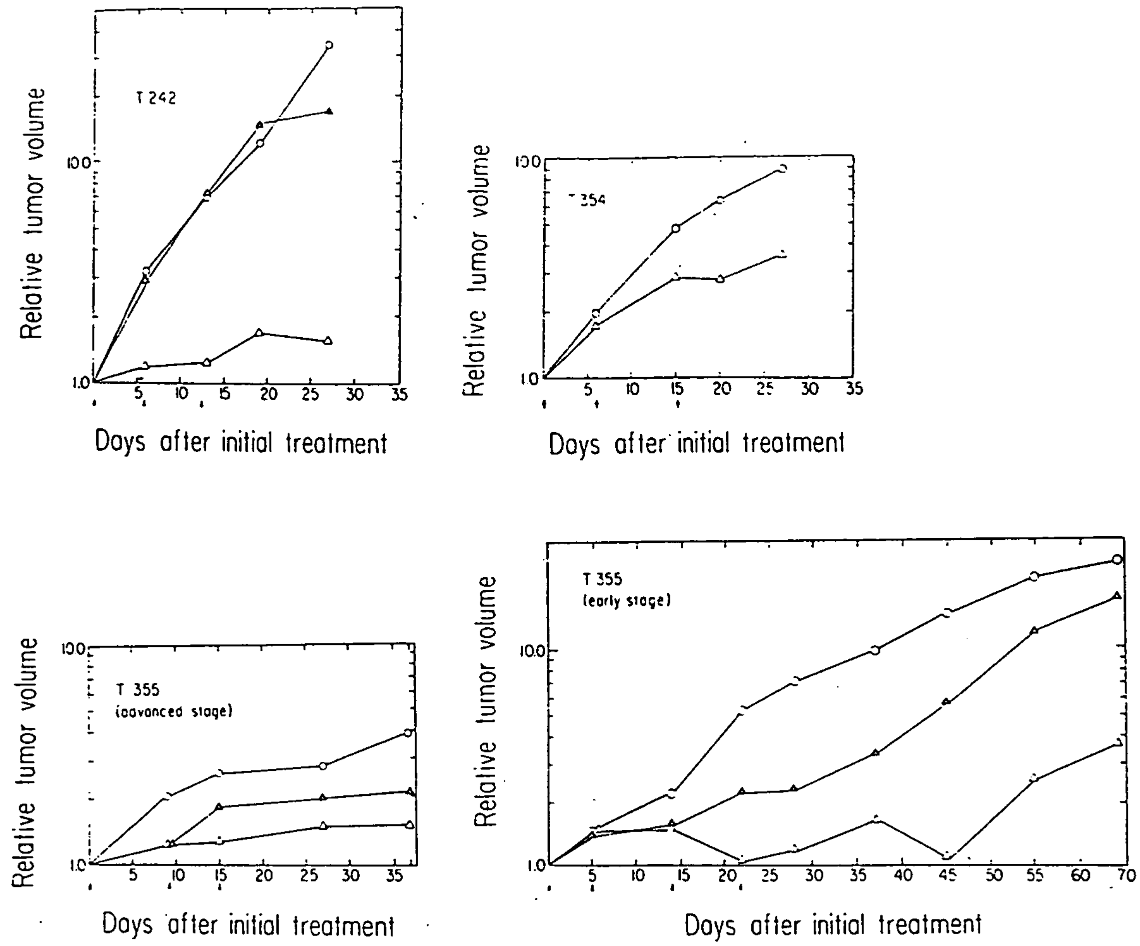

Chart 7. Response of T 242, T 354, and T 355 human melanomas in nude mice to DX. O, controls: ▲, 6 mg/kg/injection; △, 10 mg/kg/injection. *Arrows*, ɜatment.

noring the heterogeneity of sites that comprise this group of mors. However, of 7 single-agent chemotherapeutic drugs :tive against common head and neck cancer, DX has the west response percentage, 23% (10, 17, 27). In agreement :th the clinical activity in our experiments, the antitumor :tivity (Chart 11; Table 4) of DX on the growth of human rynx epidermoid carcinoma T 323 implanted into nude mice as slight and not statistically significant.

The high experimental antitumor activity of DX has been lated to the host immunological response (13, 14, 25). It was und that DX, compared to daunorubicin, has a lower effect ı the cellular compartment which is responsible for cell-meated immunity (T-cells) than on the cellular compartment sponsible for synthesis of antibodies (B-cells) (14, 36). The X activity against tumors transplanted into athymic mice ap- ːars to alter the significance of these results. Experiments are progress to test the daunorubicin activity against human mors growing in athymic mice with the aim to clarify the oblem.

ƆNCLUSIONS

From the above studies the following conclusions can be drawn: (*a*) the results of DX chemotherapy studies on a panel of human tumors xenografted into nude mice reflect the clinical response rates very closely, except in the case of the activity of DX against the melanomas and ovarian cancer; (*b*) the activity of DX differs when used against lung tumors of different histological types but is closely related to the clinical activities; and (*c*) the response of DX of the 2 (T 23 and T 198) tumors tested at the different passages was essentially the same.

Because human tumors of the same type exhibit a wide variability, their response to the anticancer drugs both in patient and in xenografts, the chemosensitivity of human tumors cannot be evaluated on the basis of the sensitivity of a few xenografts. Therefore, information about activity of antitumor drugs (old or new) can be best obtained by testing the drugs against a panel of tumors. Consequently, we are increasing the tumor numbers representing the major classes of human neoplasms in stock in our facility (actually 39).

The results indicate that there is a good correlation between the sensitivity of tumors to a drug in the human body and in BALB/c nude mice. Therefore, it is reasonable to assume that the human tumor-nude mouse system may be a suitable model for selection of drugs for the treatment of human cancer and for screening of new antitumor agents.

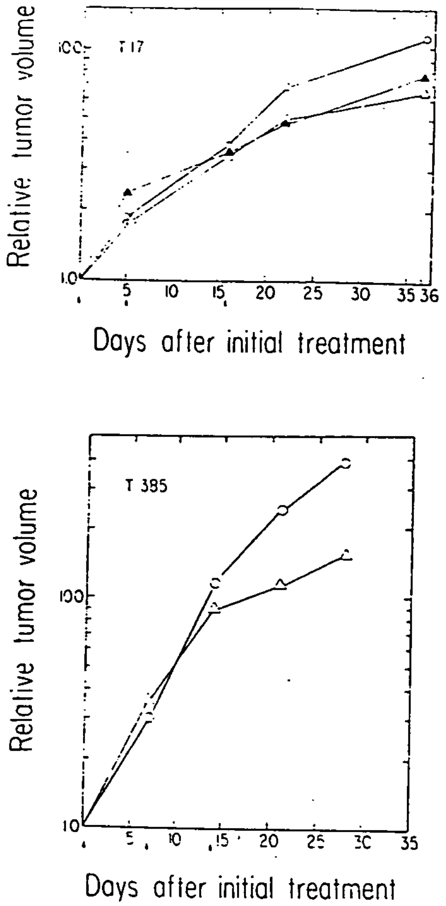

Chart 8. Response of T 17 and T 385 human ovarian tumors in nude mice to DX. O, controls; ▲, 6 mg/kg/injection; Δ, 10 mg/kg/injection. *Arrows*, treatment.

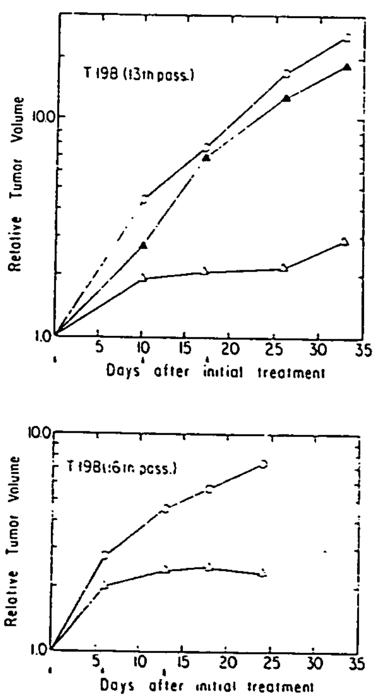

Chart 9. Response to DX of T 198 human prostate tumor in its 13th and 16th passages transplanted into nude mice. O, controls; ▲, 6 mg/kg/injection; Δ, 10 mg/kg/injection. *Arrows*, treatment.

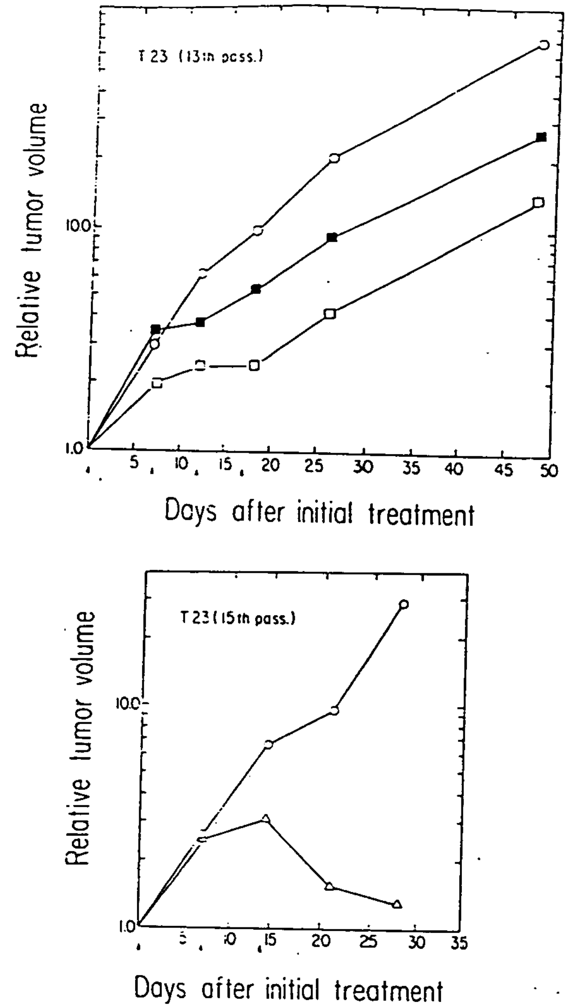

Chart 10. Response to DX of T 23 human sarcoma in its 13th and 15th passages transplanted into nude mice. O, controls; ▲, 4.4 mg/kg/injection; □, 6.6 mg/kg/injection; Δ, 10 mg/kg/injection. *Arrows*, treatment.

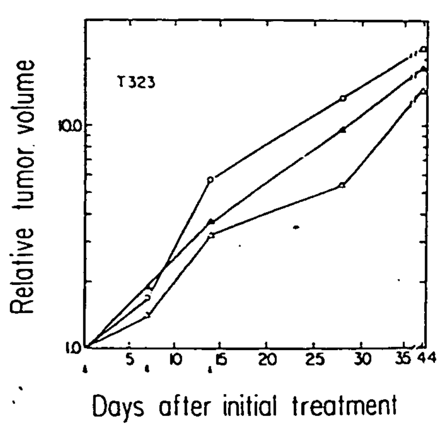

Chart 11. Response to DX of T 323 human larynx tumor transplanted into nude mice. O, controls; ▲, 6 mg/kg/injection; Δ, 10 mg/kg/injection. *Arrows*, treatment.

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